Remarks

I. Status Of The Claims And Support For The Amendment

Claims 14, 22, 52, 53, 57 and 62 have been amended.

Claims 14-22, 37, 38, 40-55, 57 and 59-72 are pending in the application, with claims 14, 22, 52, 53, 57 and 62 being the independent claims.

Support for the amendment of claims 14, 22, 52, 53, 57 and 62 is found in the Specification, for example, at page 14, lines 13, 23 and 24.

No new matter has been added by these amendments, and their entry is respectfully requested.

II. The Rejection Under 35 U.S.C. § 103 Should Be Withdrawn

At page 2 of the Office Action, the Examiner rejected claims 14-22, 37, 38, 40-55, 57 and 59-72 under 35 U.S.C. § 103(a), as allegedly being obvious over Rewinkel *et al.*, *Curr. Pharm. Design* 5: 1043-1075 (1999) (hereinafter "Rewinkel"), in view of de Nanteuil *et al.*, U.S. Patent No. 5,814,622 (hereinafter "de Nanteuil") and in further view of Adams *et al.*, U.S. Patent No. 5,780,454 (hereinafter "Adams").

Applicants respectfully traverse this rejection. A *prima facie* case of obviousness has not been established. Even if, *inter alia*, a *prima facie* case of obviousness had been established, it is rebutted by the surprising results provided by the claimed invention.

A. The Rejection

The Examiner set forth the basis for the rejection at pages 3-5 of the Office Action. The Examiner stated:

> Rewinkel et al. teach the organic component of the instantly claimed organoboronic acid salt. They also teach the boronic acid attached to the organic component in a position consistent with the structural limitations of the instant claims. However, they fail to teach the pharmaceutically acceptable salt of the boronic acid.
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> Nanteuil et al. describe compound [sic] of formula (I/g) (organoboronic acid) and pharmaceutically acceptable salts thereof (column 6, lines 20-36). The pharmaceutically acceptable salts include both base and acid addition salts. In Column 3, lines 32-34 Nanteuil et al. describe examples of counterions for base addition salts. Said examples include Sodium, Potassium and amines.
>
> Adams et al. teach boronic acid compounds of formula 1(a) which encompass the instantly claimed compounds. Adams et al. also teach pharmaceutically acceptable base addition salts (column 9, lines 47-48) which include various alkaline metal, alkaline earth metal and amine (including amino acids) salts (column 9 lines57-65).

Office Action at pages 3-4.

Applicants respectfully disagree with these conclusions and the reasoning upon which they are based. Applicants reiterate their arguments already of record, subject to the clarifications previously provided, the evidence of record, the Declaration by Dr. Kennedy filed September 26, 2007 ("the Kennedy Declaration"), and the Declaration Under 37 C.F.R. § 1.132 by Dr. Stephen Phillip Marsden filed July 30, 2008 ("the Marsden Declaration"). Applicants also provide the following additional comments with respect to this rejection.

B. A Prima Facie Case Of Obviousness Has Not Been Established

In order for an obviousness rejection to be proper, it is necessary for the Examiner to identify reasons why one of ordinary skill in the art would have combined

the cited art in an effort to obtain the claimed invention. *See KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1741 (2007) ("[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."). It is respectfully submitted that inadequate reasons have been provided in the Office Action as to why one of ordinary skill in the art would have combined the cited art in an effort to obtain the claimed invention, as currently presented.

Independent claim 14 recites that the base addition salt is more stable to deboronation than the corresponding free acid. The other independent claims contain similar recitations. No reasons have been proffered by the Examiner as to why one of ordinary skill in the art would have made a base addition salt of the boronic acids recited in the claims, wherein the salt is more stable to deboronation than the corresponding free acid.

Boronic acids are known to be unstable, and exhibit oxidative degradation at the C-B bond. *See* the Marsden Declaration at paragraphs 5 and 8. Furthermore, since boronic acids are weak acids, a boronic acid in a strong alkaline solution, such as would have been used to make an alkaline base addition salt, would have been expected to form a basic solution that would have been unstable. *See* the Kennedy Declaration at paragraph 25. *See also* the Specification at page 5, lines 22-29.

Under *KSR*, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield *predictable results*." *KSR* at 1739 (emphasis added). Here, the claimed invention, which is a base addition salt of a boronic acid that is more stable to deboronation than the corresponding free acid, would not have

been a predictable result. Evidence for this is found in Davies, G., "Changing The Salt, Changing The Drug," *The Pharmaceutical Journal 266*: 322-323 (2001) ("Davies"), which the Examiner referred to at page 4 of the Office Action.

Although Davies discloses in the first sentence that "[c]hanging a drug from its free base or acid to a salt form is commonly done to improve its kinetics, absorption or physicochemical properties (eg., stability hygrosopicity and flowability)," Davies also stated:

> There is, as yet, *no reliable way of predicting exactly what effect changing the salt form of an active drug will have on its biological activity*, and the supposition that the same salt form of two related parent compounds will behave in exactly the same way may not be correct.

Davies at page 322, second paragraph (emphasis added).

Thus, the Examiner's reliance on Davies for the proposition that "one would have been motivated to prepare a salt of the organoboronic acid 21 described by Rewinkel et al." and that "[s]uch a modification would not be new to the art" is misplaced, with respect to the invention as currently claimed. Davies itself teaches one of ordinary skill in the art that a particular feature, such as increased stability due to decreased deboronation, could not have been predicted. Therefore, under *KSR*, the cited art would not have predicted the claimed invention, and the claimed invention would have been nonobvious.[1]

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[1] In the Kennedy Declaration, Dr. Kennedy discussed Davies. For example, *see* paragraph 9, 28, 29 and 35 of his Declaration. The discussion herein is complementary to the discussion of Davies by Dr. Kennedy. Whereas Dr. Kennedy explained that Davies did not discuss boronic acids, the discussion herein establishes that Davies itself supports Applicants' argument that it would not have been predicted by Rewinkel, de Nanteuil and Adams that making a base addition salt of a boronic acid would have promoted increased stability to deboronation.

Rewinkel depicts a boronic acid in structure 21 at page 1052. However, Rewinkel fails to disclose that a base addition salt would specifically increase the stability of the boronic acid to deboronation.

de Nanteuil and Adams fail to cure the deficiency of Rewinkel. De Nanteuil depicts a boronic acid structure (I/g) at column 6. At column 3, lines 23-24, de Nanteuil discloses "addition salts thereof with a pharmaceutically acceptable acid or base." At column 3, lines 31-34, de Nanteuil discloses that "[a]mong the pharmaceutically acceptable bases which may be mentioned without any limitation are sodium hydroxide, potassium hydroxide, triethylamine, ter-butylamine, etc." However, de Nanteuil fails to disclose that formation of a base addition salt would specifically increase the stability of the boronic acid to deboronation.

Adams depicts a boronic acid structure (1a) a column 4. Adams also provides a general disclosure of base addition salts at column 9, lines 47-65. However, Adams fails to disclose that formation of a base addition salt would specifically increase the stability of the boronic acid to deboronation.

Given the unpredictability, as evidenced by Davies, of how a base addition salt might or might not affect a particular feature of a boronic acid salt formulation such as stability due to deboronation, Rewinkel, de Nanteuil and Adams would not have provided a reasonable expectation of success in obtaining the claimed invention. Indeed, even in 2007, *i.e.*, four years after the present application was filed, when those of ordinary skill attempted to stabilize boronic acids, they used protecting groups, rather than forming base addition salts from the free acid. *See* WO 2009/014550 A1, *e.g.*, at paragraphs [05]-[09]. This document is the published version of application no.

PCT/US2007/084156, filed November 8, 2007. A copy of WO 2009/014550 A1 is being filed herewith as Exhibit A.

Hence, even in combination, Rewinkel, de Nanteuil and Adams would not have predictably provided the claimed invention. Therefore, a *prima facie* case of obviousness has not been established over Rewinkel, de Nanteuil and Adams.

C. The Claimed Invention Provides Surprising Results

Even if a *prima facie* case of obviousness had been established, and it has not, the claimed invention provides unexpected results sufficient to rebut the rejection. Specifically, the presently claimed invention is a base addition salt of a boronic acid that is more stable to deboronation than the corresponding boronic acid.

Given (1) the unstable nature of boronic acids, as evidenced by the Specification, the Kennedy Declaration and the Marsden Declaration, and (2) the unpredictability of the results of formulating a free boronic acid as a base addition salt, as evidenced by Davies, it would have been surprising if forming a base addition salt would have resulted in a salt that is more stable to deboronation than the corresponding free boronic acid. Yet, as shown in Examples 27 and 28 of the present Specification, and as discussed in paragraphs 32-34 of the Kennedy Declaration, the claimed base addition salts are more stable than the corresponding free boronic acid. This result is surprising and would not have been predicted by Rewinkel, de Nanteuil and Adams.

For at least these additional reasons, even in combination, Rewinkel, de Nanteuil and Adams would not have provided the claimed invention.

Applicants respectfully request that this rejection be reconsidered and withdrawn.

III. The Rejection For Obviousness-Type Double Patenting

At page 8 of the Office Action, the Examiner rejected claims 14-22, 37, 38, 40-55, 57 and 59-72 for non-statutory obviousness-type double patenting over claims 1-21, 23, 25, 50-56 and 71-73 of U.S. Patent No. 7,112,572. Applicants respectfully request that this rejection be held in abeyance until the Examiner has identified otherwise allowable subject matter in the present application. At such time, Applicants will consider filing a terminal disclaimer to obviate this rejection.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the presently outstanding rejections.

Applicants believe that a full and complete reply has been made to the outstanding Office Action. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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